REMARKS

Claims 1, 4-10, and 14-24 are pending. Claims 9 and 19 are withdrawn from consideration. Claims 10, 14, and 24 are allowed. Claims 8 and 18 are rejected under 35 U.S.C. § 101, claims 5, 9, 15-17, and 20 are rejected under 35 U.S.C. § 112, second paragraph, and claims 1, 4, 6-8, 20, and 23 are rejected under 35 U.S.C. § 103. Claims 21 and 22 are objected to. Applicants address each of these rejections below.

Amendments

The amendments presented herein address issues raised in the current Office Action. In particular, the specification has been amended to capitalize the trademarks recited at pages 16, 22, 29, and 34, of the English language specification. These trademarks are also accompanied by generic terminology. As evidenced by enclosed Exhibit 1, one skilled in the art would recognize that RETRONECTIN is a recombinant human fibronectin.

Further, in accordance with the Office's request, the quotation marks have been deleted from claims 5, 9, 15, 16, 17, 19, and 20. Next, in accordance with the Office's suggestion, the cell of claims 8 and 18 has been defined as "isolated". Support for this amendment is found in the specification as originally filed, for example, at page 13, lines 12-14 and page 22, lines 17-21, of the English language specification. Finally, claim 10 has been amended to provide antecedent basis for the recitation for the location of the

exogenous gene with respect to the gene encoding the fusion protein in dependent claim 17. Applicants respectfully submit that no new matter has been added by these amendments.

Pursuant to this amendment, claims 1, 4-10, and 14-24 are pending in the application. While the Office, in the Office Action Summary, indicates that claims 9 and 19 have been withdrawn from consideration, Applicants submit that the Office has considered claim 9 at least in part. (See, for example, page 4, paragraph 2, of the current Office Action.) Clarification is requested.

Rejection under 35 U.S.C. § 101

Claims 8 and 18 are rejected under 35 U.S.C. § 101 for being directed to non-statutory subject matter. The Office asserts that the claims encompass naturally occurring products. To expedite prosecution, as noted above, claims 8 and 18 have been amended to be directed to an isolated cell. The § 101 rejection should be withdrawn.

Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 5, 9, 15-17, and 20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Office notes that claims 5, 9, 15-17, and 20 contain quotation marks that, according to the Office, confuse the scope of the claim. None of the

pending claims, as amended, contain quotation marks. This basis for rejection should be withdrawn.

Claim 17 also is rejected based on the assertion that the claim limitation "located on separate molecules" lacks antecedent basis. Applicants note that a vector may contain multiple DNA molecules (e.g., plasmids, naked DNA, etc.). Accordingly, Applicants disagree that claim 10 requires that "[a]ll the genes are contained within the same molecule." Rather, when given the broadest reasonable interpretation, claim 10 encompasses both a single vector carrying a single DNA molecule, containing both the foreign gene and the fusion protein DNA, and a single vector carrying multiple DNA molecules, one containing the foreign gene of interest and another containing the fusion protein gene. Nevertheless, to expedite prosecution and clarify the scope of the claim, Applicants have amended claim 10 to specifically state that the exogenous gene and the DNA encoding a fusion protein "may be located on the same or different molecules." As such, claim 10 provides express antecedent support for the recitation of dependent claim 17. The § 112, second paragraph rejection of claim 17 should be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 1, 4, 6-8, 20, and 23 stand rejected under 35 U.S.C. § 103 as being obvious over Gurney et al. (Proc. Natl. Acad. Sci. USA 92:5292-5296, 1995; "Gurney") in view of Wang et al. (J. Biol. Chem. 270:23322-23329, 1995; "Wang") for the reasons set forth

in the last Office Action. In addition, the Office newly rejects claims 1, 4, 6-8, 20, and 23 under 35 U.S.C. § 103 for being obvious over Gurney in view of Jackson et al. (EMBO J. 12:2809-2819, 1993; "Jackson"). In particular, the Office asserts that the estrogen receptor ("ER") is a useful substitution for the growth hormone receptor ("GHR") and that one skilled would have been motivated to exchange Gurney's GHR for Wang's or Jackson's ER to arrive at the invention as claimed. As such, the Office finds the claimed fusion protein to be obvious in view of the combination of Gurney and Wang or Jackson.

Prior art references can be modified or combined to reject claims as *prima facie* obvious, so long as there is a reasonable expectation of success (M.P.E.P. § 2143.02 (Eighth Edition, Rev. 2, May 2004) citing *In re Merck & Co.*, Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); emphasis added). While obviousness does not require absolute predictability, at least some degree of predictability is required. In the instant case, Applicants respectfully submit that, given the state of the art at the time of invention, one could not have reasonably predicted that the modifications proposed by the Office would yield a functional fusion protein.

Turning to Gurney, Applicants note that the goal of the Gurney study was to "examine the mechanisms of c-Mpl signal transduction" (see, e.g., first full paragraph, right column, page 5292). To that end, Gurney studied a series of chimeric receptors containing deletions within the c-Mpl intracellular domain. Gurney's investigations revealed that a chimeric receptor, comprised of the extracellular domain (i.e., ligand

binding domain) of the human growth hormone receptor and the intracellular domain (i.e., proliferation inducing domain) of c-Mpl, the thrombopoietin (TPO) receptor, retained the proliferative and cell signaling activities of the native c-Mpl receptor. Importantly, Applicants note that both components of the chimeric receptor belong to the cytokine receptor superfamily. In fact, one of the primary discoveries noted by Gurney is that, although they lack significant sequence identity, "many members of the cytokine receptor superfamily now appear to possess similar functional architecture" (see, e.g., second full paragraph, left column, page 5296). For example, it appears that the conserved "membrane proximal region including box 1 is required for mediating a proliferative response." Gurney thus concludes that "the growth signal induced by c-Mpl is likely to involve a mechanism similar to that used by other members of the cytokine receptor family."

Given this context, there is no reason to expect that a fusion protein comprised of two *divergent* receptor components would similarly maintain its functionality. In other words, since GHR and c-Mpl possess similar "functional architecture," one can reasonably expect that replacing the ligand binding domain of c-Mpl with the ligand domain of another cytokine receptor would yield a functional chimera; however, the same cannot be said for a chimera comprised of non-analogous components, as is the case in the presently claimed invention. As noted previously, both GHR and c-mpl are *transmembrane (or plasma membrane)* cytokine receptors, single-pass transmembrane

proteins embedded in the plasma membrane that activate upon homodimerization via the JAK/STAT pathway. Conversely, steroid hormone receptors, such as an estrogen receptor are an *intracellular (or nuclear)* receptor, confined exclusively to the cytosol and nucleus. As discussed previously and in detail below, these two protein families have substantially different structures as well as divergent ligand binding and signal transduction mechanisms.

In terms of dimers formed, while GHR and ER indeed both form "dimers" upon ligand binding, the dimers formed are dramatically different, not only in terms of structure and composition, but also in terms of subsequent activity. For example, whereas the GHR dimer is comprised of a single GH ligand bound to two adjacent GHR molecules, the ER dimer is comprised of two activated receptors (e.g., two separate estrogen receptors, each bound to a single estrogen molecule.)

In terms of ligands bound, a plasma membrane receptor, such as GHR, binds a *water soluble* ligand, such as GH, via cell surface receptor molecules. Conversely, a nuclear receptor, such as ER, binds a *lipid soluble* ligand, such as estrogen, that enters the cell and binds to the nuclear receptor molecule.

In terms of structure, plasma membrane receptors are comprised of an extracellular domain that binds the ligand, a hydrophobic transmembrane domain that anchors the receptor in the membrane, and a cytoplasmic that gets activated when the ligand binds the extracellular domain. Conversely, a nuclear receptor, such as a steroid hormone receptor,

is comprised of a variable domain that activates the promoters of the genes being controlled, a zinc-finger domain needed for DNA binding to the response element, and a ligand binding domain for binding the particular hormone as well as the second unit of the dimer.

In terms of signal transduction, activation of a plasma membrane receptor begins with binding of the ligand via an extracellular domain. Binding of the ligand activates a cytoplasmic domain by either a change in receptor shape or a change in the state of receptor aggregation. With GHR in particular, a single GH ligand binds to two adjacent GHR receptors to form an active dimer. The activated dimer is a tyrosine kinase, an enzyme that attaches phosphate groups to certain tyrosine residues — first on itself, then on other proteins converting them into an active state and thus beginning the signal transduction cascade. Many of these other proteins are also tyrosine kinases and in this way a cascade of expanding phosphorylations occurs within the cytosol. Some of these cytosolic tyrosine kinases act directly on gene transcription by entering the nucleus and transferring their phosphate to transcription factors, thus activating them; others act indirectly through the production of second messengers.

Conversely, signal transduction with a nuclear receptor begins with the ligand (e.g., a steroid hormone such as estrogen) passing into the cell and binding to the receptor. The receptor is activated through ligand binding, whereupon it binds to a second copy of itself to form a homodimeric complex. The complex releases histone

deacetylase (HDAC) and recruits histone acetylase (HAT) relieving chromosome repression. The complex then binds to a specific DNA sequence (i.e., a steroid response element) in the promoter region of a gene to turn on transcription thereof.

Given these differences, one skilled in the art would not have regarded GHR and ER to be obvious, readily interchangeable equivalents. Moreover, as noted below, at the time of invention, there was no reason to believe that domains from two distinct receptor families could be seamlessly combined to yield a functional fusion protein. Thus, one skilled in the art would not have reasonably expected the dimerization of a steroid hormone receptor, such as an estrogen receptor, to activate the c-Mpl receptor in a manner analogous to that of a growth hormone receptor or other cytokine receptor. Thus, the presently claimed invention is non-obvious over the combination of Gurney and Wang.

***

Turning to the Jackson reference, which describes fusion proteins of c-Abl, Applicants note that c-Abl is a non-receptor-type tyrosine kinase. In contrast to c-Mpl, whose signal transduction occurs after ligand binding, the inductive signals and mechanisms associated with c-Abl were less defined given that Jackson hypothesizes possible mechanisms for the activation of c-Abl (see, e.g., right column, page 2817). Jackson notes that it was "[c]ompletely unexpected ... that a non-transforming, normal c-Abl derivative could be activated for transformation by fusion to the ER HBD [Hormone

Binding Domain]" (see, e.g., left column, page 2817). Jackson further notes that "activation by the ER HBD is relatively specific because C-terminal fusion of other proteins, including Gag, Bcr, and the ecdysone receptor HBD did not activate c-Abl" (see, e.g., left column, page 2817). The fact that c-Abl was not activated by other dimerizing receptors and that dimerization is not generally seen in non-receptor type molecules suggests that the activation process involves another mechanism, such as the association with a heat shock protein (HSP90) (see, e.g., right column, page 2809). In any event, the unique and unexpected nature of the Jackson findings does not support the Office's suggestion that all dimerizing receptors are interchangeable equivalents.

Applicants further submit that not only would one skilled in that art not have any reasonable expectation of success, but also that combining the references as suggested by the Office would result in a non-functional chimera. In particular, the Office states in the current Office Action, at page 6, that "a person of ordinary skill in the art would have expected that the estrogen receptor as taught by Jackson *et al.* would be a useful substitution for the GHR as taught by Gurney *et al.*" Following this logic when combining the teachings of Jackson and Gurney, one skilled in the art would have simply replaced the ligand binding domain of the growth hormone receptor with the ligand binding domain of the estrogen receptor, thereby yielding a fusion protein containing the ER HBD and intracellular domain of c-Mpl. However, as Applicants discovered, simple fusion of a receptor with ER does not automatically lead to activation. In fact, it appears

that the tertiary structure of the extracellular domain is critical. (See Nagashima et al., *Biochem. Biophys. Res. Commun.* 303:170-176, 2003; "Nagashima;" a copy of which is provided herewith as Exhibit 2.) In an attempt to restrict the reactivity of the fusion protein to estrogen alone (i.e., suppress TPO activation), Nagashima deleted various peptide chains from the extracellular region of c-Mpl (see Table 1 of Nagashima). In the process, however, Nagashima discovered that, although reactivity towards TPO was abolished, so was the reactivity towards estrogen. Accordingly, deletion of all or part of the extracellular region of c-Mpl rendered the molecule unresponsive towards estrogen.

If a proposed modification renders the prior art invention being modified unsatisfactory for its intended purpose, then there can be no suggestion of motivation to make the proposed modification. (See M.P.E.P. § 2143.01 (Eighth Edition, Rev. 2, May 2004) under the heading "The Proposed Modification Cannot Render The Prior Art Unsatisfactory For Its Intended Purpose," citing *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)). As Nagashima demonstrates, a fusion protein resulting from the suggested combination of the prior art references, i.e., comprised of the hormone binding domain of the estrogen receptor and the proliferation inducing domain of c-Mpl, would not be activated by estrogen, and, therefore, would be unsuitable for its intended purpose. Given the failings noted by Nagashima, Applicants respectfully submit that there is no suggestion or motivation to combine the teachings of the prior art as suggested by the Office.

In sum, Applicants respectfully submit that not only is there no motivation to modify or combine the references as suggested by Office, but that any such combination would not have a reasonable expectation of success. Accordingly, Applicants respectfully submit that the Office's conclusion of obviousness is in error and respectfully request reconsideration of the § 103 rejection in light of the comments herein.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and this action is hereby respectfully requested.

Enclosed are a Petition to extend the period for replying to the Office Action for three (3) months, to and including September 14, 2005, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 14 September 2005

James D. DeCamp, Ph.D.
Reg. No. 43,580

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045